PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 15037/WO/02	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IL 03/00764	International filing date *(day/month/year)* 24.09.2003	Priority date *(day/month/year)* 26.09.2002
International Patent Classification (IPC) or both national classification and IPC C12Q1/68		
Applicant YISSUM RESEARCH DEVELOPMENT COMPANY OF ... et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.04.2004	27.12.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Bradbrook, D Telephone No. +49 89 2399-7413

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IL 03/00764

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-45 as originally filed

Claims, Numbers

1-5 as originally filed

Drawings, Sheets

1/16-16/16 as originally filed

2. With regard to the **language,** all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-4(partially),5(fully)

because:

☒ the said international application, or the said claims Nos. 3 for IA relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-4(partially),5(fully)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-4
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	1-4
	No:	Claims	-
Industrial applicability (IA)	Yes:	Claims	1,2,4
	No:	Claims	-

2. Citations and explanations

see separate sheet

Section I

1. Sequence listing pages 1-2, filed with the letter of 13.04.04, do not form part of the application (Rule 13ter.1(f) PCT).

Section III

1. Subject-matter for which no international search report has been established have not been examined (cf Rule 66.1 PCT). Therefore, no opinion is provided with respect to the provisions of Art.33(1) PCT (i.e. novelty, inventive step and industrial applicability) for claim 5. Moreover, claims 1-4 are examined only insofar as the term "Parkinson's Disease (PD)-susceptibility haplotype" refers to the presence of PON1 alleles L55M and Q192R and ACHE alleles delHNF3, H332N and P446, as indicated on p.19, last three lines, of the description.

2. Claim 3 comprises a step of providing a blood sample from an individual, which is considered by this Authority to encompass a surgical procedure carried out on the human or animal body, and therefore is covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of said claim (Article 34(4)(a)(i) PCT).

Section V

1. Reference is made to the following documents:

   D1: Kondo et al., Brain Res., Vol.806, p.271-273 (1998)
   D2: Carmine et al., Mov.Disord., Vol.17, p.764 (2002)
   D3: Bartels et al., Am.J.Hum.Genet., Vol.52, p.928-936 (1993)
   D4 Shapira et al., Hum.Mol.Genet., Vol.9, p.1273-1281 (2000)
   D5: Kaufer et al., Curr.Opin.Neurol., Vol.12, p.739-743 (1999)

2. Novelty and Inventive step (Art.33(2) and (3) PCT)

2.1 The available prior art does not disclose an association between the PON1/ACHE haplotype of the present application and the risk or incidence of Parkinson's Disease.

Therefore, the subject-matter of claims 1-4 would appear to be novel (Art.33(2) PCT).

2.2 The prior art contains various reports indicating associations between individual PON1 polymorphisms and Parkinson's Disease (e.g. D1, D2: abstracts). Furthermore, the significance of impaired ACHE function in Parkinson's Disease has also been recognized (D5: p.740, col.2, para.3-4), as have polymorphisms in the ACHE gene and possible linkage between certain of these (cf D3: Fig. 2 and p.933-934 bridging para.; D4: abstract). However, there was no reason for the skilled person to suppose that a common haplotype linking polymorphisms of the two genes may provide a tool for predicting the susceptibility to PD in a population. Therefore, notwithstanding the objections under Art.6 PCT (cf item 3, infra), the subject-matter of claims 1-4 appears to involve a inventive step (Art.33(3) PCT).

3 The present application is directed to a haplotype which apparently acts as a tool for determining a genetic predisposition to PD. However, the experimental data is rather unclear.

3.1 Example 4 purports to show that PD patients have a common genotype, yet of the six subjects shown in Table 13, two differ (patient 40: hom at P446; patient 1007: M/M at 55 and Q/Q at 192). Moreover, such a study of genotypes does not provide any information on the haplotypes present, because it does not relate the allelic identities to the chromosomes. In Example 6 it is stated that the rare haplotype was strongly over-represented in the exposed PD samples, yet this is not seen in Fig.14, to which Example 6 refers (p.42-43: bridging paragraph). Furthermore, the haplotypes in Tables 14a-c of Example 6 are not defined.

3.2 Whilst it is stated in Example 4 that "Interestingly, the haplotype including the PON1 55/192 mutations, and the ACHE HNF/yt/P446 polymorphisms ... is the predominant amongst PD patients", this is not demonstrated by any of the experimental results, and there is no demonstration that the determination of the haplotype in question can in fact be used to assess predisposition to PD. This inference appears to arise from a combination of the linkage studies and the association studies for the individual SNPs, show in the experimental results.

3.3 Therefore, the subject-matter of claims 1-4 is not properly supported as required by

Art.6 PCT.

4. Clarity (Art.6 PCT)

4.1 The term "by appropriate means", used in claims 3 and 4 is unclear (Art. 6 PCT)

4.2 Claim 4 is unclear (Art. 6 PCT) as it relates to a method for testing a blood sample for the presence of the PD-susceptibility haplotype, yet does not define how this is carried out.

4.3 The meaning of the claims should be clear from the wording of the claims alone in order to satisfy the requirements of Art.6 PCT (cf PCT Guidelines, III-4.2). Therefore, as claims 1-4 appear to relate to the analysis of DNA, the haplotype should have been defined with respect to the nucleotide polymorphisms.

5. Industrial applicability (Article 33(4) PCT)

5.1 For the assessment of the present claim 3 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims.